IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

PHARMACEUTICAL MANUFACTURING RESEARCH SERVICES, INC.,

Plaintiff-Petitioner,

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION, SCOTT GOTTLIEB, M.D., in his official capacity as the Commissioner of Food and Drugs, and his successors and assigns, and ERIC D. HARGAN, in his official capacity as the Acting Secretary of the United States Department of Health and Human Services, as well as his successors and assigns,

Defendants,

and

DAIICHI SANKYO, INC.,

Intervenor-Defendant.

CIVIL ACTION
NO. 17-04898

PAPPERT, J. **January 22, 2019**

MEMORANDUM

On April 20, 2017, the Food and Drug Administration approved RoxyBond, an immediate release opioid labeled for abuse deterrence. Pharmaceutical Manufacturing Research Services, Inc. intends someday to market its own abuse-deterrent product. It petitioned the FDA to stay the approval of RoxyBond until the FDA addressed the merits of PMRS's pending Citizen Petitions, which raise concerns about the FDA's approval process for opioids. The FDA denied PMRS's Petition for Stay, finding that PMRS failed to meet the requisite statutory showing.

PMRS now seeks review of the FDA's decision, alleging that the FDA's denial of PMRS's Petition for Stay was "arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). All parties—PMRS, the FDA and intervenor-defendant Daiichi Sankyo—moved for summary judgment. For the reasons that follow, the Court dismisses PMRS's Amended Complaint for lack of jurisdiction because PMRS lacks Article III standing.

I

A

PMRS is a corporation involved in the research and development of opioid medications, in particular opioids with abuse-deterrent properties. (Am. Compl. ¶ 14.) In two separate Citizen Petitions[1] dated February 19, 2016 and March 6, 2017, PMRS made recommendations to the FDA to "remedy the critical issues with FDA's approach to opioids." (Citizen Petition, AR at FDA00708–29; Citizen Petition, AR at FDA00408–17.) In its 2016 Citizen Petition, PMRS criticized the types of studies required by the FDA to evaluate abuse-deterrent formulations. In its 2017 Petition, PMRS asked the FDA to revoke approval for all opioid products labeled for the treatment of chronic pain. (Citizen Petition, AR at FDA00408.)

The FDA issued interim responses to both Citizen Petitions, stating that because they raised complex issues requiring extensive review and analysis, the FDA had not reached a decision on the Petitions but would respond fully once it did. *See* (FDA

[1] The FDA permits private entities to provide comments and opinions by filing Citizen Petitions. 21 C.F.R. § 10.30. Citizen Petitions may be filed by any interested person and may ask the FDA to "issue, amend, or revoke a regulation or order[,] or take or refrain from taking any other form of administrative action." *See Sheller, P.C. v. United States Dep't of Health & Human Servs.*, 663 F. App'x 150, 153 (3d Cir. 2016) (citing 21 C.F.R. §§ 10.25(a), 10.30).

Response, AR at FDA00991; FDA Response, AR at FDA00705). On December 20, 2018, the FDA denied PMRS's February 2016 Petition, disagreeing with PMRS's critiques of the studies required for abuse-deterrent labeling. *See* (Notice of Response to Citizen Petitions Ex. A, ECF No. 69). PMRS's March 2017 Citizen Petition regarding chronic-use labeling remains pending.

B

In October 2016, Inspirion Delivery Services, LLC. submitted a New Drug Application ("NDA") to the FDA for RoxyBond, an immediate release opioid with abuse-deterrent properties. (RoxyBond Briefing Document, AR at FDA00117.) To deter abuse, RoxyBond imparts physical and chemical barriers that make it more difficult and less rewarding to abuse intranasally and intravenously. *See* (CDER Summary Review, AR at FDA01070). For example, RoxyBond resists particle size reduction with common household tools, making it harder for users to crush the tablet and snort it. *See* (*id*. at FDA01077). The FDA approved RoxyBond on April 20, 2017 through the 505(b)(2) pathway to the Food, Drug & Cosmetic Act,[2] making RoxyBond the first immediate release opioid approved by the FDA for chronic use with abuse-deterrent properties. (CDER Summary Review, AR at FDA1074.)

[2] A manufacturer can obtain FDA approval via three different application pathways, one of which is the Section 505(b)(2) NDA. An applicant for a 505(b)(2) NDA can receive approval for marketing a new drug even where one or more investigations relied upon for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted." *See In re Egalet Corp. Sec. Litig.*, 340 F. Supp. 3d 479, 485 (E.D. Pa. 2018) (citing 21 U.S.C. § 355(b)(2)). Thus, a 505(b)(2) NDA applicant can rely on previously published reports of studies and the FDA's own findings with respect to drugs that the FDA has previously approved. (*Id.*)

C

After the FDA approved RoxyBond, PMRS filed a Petition for Stay of Action ("PSA") with the FDA pursuant to a regulation which provides that "[a]n interested person may request the Commissioner to stay the effective date of any administrative action." 21 C.F.R. § 10.35. In short, PMRS argued that the FDA should stay the approval date of RoxyBond until the agency issued substantive written responses to PMRS's pending Citizen Petitions. *See* (Petition for Stay of Action, AR at FDA00001).

On October 19, 2017, the FDA denied PMRS's PSA. (FDA Response to Petition for Stay, AR at FDA00372–9.) The FDA concluded that PMRS failed to meet the requisite statutory showing for a stay under 21 C.F.R. § 10.35(e), namely: (1) that PMRS will suffer irreparable injury; (2) that PMRS demonstrated sound public policy grounds supporting the stay and (3) that the delay resulting from the stay was outweighed by public health or other public interests. (*Id*.)

While this was ongoing, PMRS submitted an NDA for its own abuse-deterrent, immediate release opioid. *See* (DS Mot. Summ. J. Ex. A at 3, ECF No 37-4). Unlike RoxyBond, PMRS's proposed drug was intended for acute, as opposed to chronic, use. (*Id*.) PMRS claimed that its product would deter abuse by injection because a solution prepared from the tablets would have a dark, opaque, "contaminated-looking" appearance. *See* (FDA Denial of PMRS's New Drug Application at 1, ECF No. 58-2).

On November 16, 2017, the FDA's Center for Drug Evaluation and Research ("CDER") issued a complete response letter to PMRS concluding that PMRS's NDA could not be approved in its present form for "multiple reasons." *See* (Proposal To

Refuse To Approve PMRS's New Drug Application, ECF No. 37-4 at 4).[3] The letter also described deficiencies relating to the chemistry, manufacturing and controls requirements. (*Id.*)

The FDA denied PMRS's NDA and request for a hearing on October 30, 2018, (Denial of PMRS's New Drug Application Ex. A, ECF No. 58-2), stating that PMRS lacked sufficient and reliable evidence supporting its proposed abuse-deterrence labeling. (*Id.* at 3.) The FDA further found that PMRS's proposed labeling was false and misleading under section 505(d)(7) of the Food, Drug & Cosmetic Act. (*Id.*)

D

After the FDA denied PMRS's Petition to Stay RoxyBond's approval, PMRS filed this lawsuit under the Administrative Procedure Act, 5 U.S.C. § 701. PMRS seeks declaratory, injunctive and other equitable relief against the FDA, Scott Gottlieb in his official capacity as Commissioner of the FDA and Eric D. Hargan in his official capacity as the Acting Secretary of the United States Department of Health and Human Services. (Am. Compl., ECF No. 11.) In addition to arguing that the denial was "arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law," *see* (*id.* ¶ 2) (citing 5 U.S.C. § 706(2)(A)), PMRS asks the Court to stay the

[3] Those reasons included that: (1) the oxycodone in the formulation could be readily extracted in commonly available solvents into a solution suitable for injection; (2) there was insufficient data showing the presence of excipients (including dye) in the formulation that could be expected to deter abuse by injection; (3) the data submitted was insufficient to show the product was meaningfully resistant to manipulation for misuse or abuse; (4) there was no data submitted, including data from pharmacokinetic and human abuse liability studies, fully characterizing the product's abuse potential by all relevant routes of abuse and (5) the data submitted was not sufficient to rule out the possibility that the proposed formulation could result in a greater proportion of abuse by injection of PMRS's product compared to a conventional immediate release oxycodone formulation. (*Id.*)

effective date of RoxyBond until the FDA issues a substantive response to PMRS's Citizen Petitions.[4]

On November 15, 2017, Daiichi Sankyo, RoxyBond's exclusive United States marketer and distributor, moved to intervene as a defendant. (Mot. Intervene, ECF No. 6.) The Court granted the Motion on January 23, 2018. (Order, ECF No. 19.)

All parties filed Motions for Summary Judgment. *See* (Pl. Mot. Summ. J., ECF No. 34; FDA Mot. Summ. J., ECF No. 36; DS Mot. Summ. J., ECF No. 37). The FDA argued that judgment should be entered in its favor because the FDA's denial of PMRS's PSA was not arbitrary and capricious. Daiichi Sankyo contended that, in addition to the FDA's merits argument, PMRS lacked constitutional standing. Specifically, Daiichi Sankyo claimed that PMRS failed to show it suffered an injury in fact from the FDA's denial of the PSA. During oral argument on the Motions, the Court asked the FDA and PMRS to submit supplemental briefing on Daiichi Sankyo's standing argument, which the parties did shortly thereafter. *See* (FDA Letter, ECF No. 62; PMRS Letter, ECF No. 65; DS Letter, ECF No. 67).

II

Article III of the United States Constitution limits the exercise of judicial power to cases and controversies. *Clapper v. Amnesty Int'l USA*, 568 U.S. 398, 408 (2013). The case-or-controversy requirement demands that plaintiffs "establish that they have standing to sue." *Id.* (citing *Raines v. Byrd*, 521 U.S. 811, 818 (1997)).

[4] The FDA issued a substantive response to PMRS's February 2016 Citizen Petition on December 20, 2018. However, PMRS's March 2017 Citizen Petition regarding chronic use labeling remains pending.

There are three elements that must be met to establish Article III standing. The plaintiff must have (1) suffered an injury in fact, (2) that is fairly traceable to the challenged conduct of the defendant, and (3) that is likely to be redressed by a favorable judicial decision. *Lujan v. Defs. of Wildlife*, 504 U.S. 555, 560–561 (1992) (internal citations and quotations omitted).

After meeting these elements, the plaintiff must also satisfy certain judicially imposed, prudential requirements. For example, a plaintiff seeking to enforce a statute must be within the zone of interests that the statute protects. *Bennett v. Spear*, 520 U.S. 154, 162 (1997). Although Congress may modify these prudential requirements, Congress may not change or undermine Article III. *See id.*

The party invoking federal jurisdiction bears the burden of establishing these elements. *See FW/PBS, Inc. v. Dallas*, 493 U.S. 215, 231 (1990). Since the elements of standing are "not mere pleading requirements but rather an indispensable part of the plaintiff's case," each element must be supported in the "same way as any other matter on which the plaintiff bears the burden of proof, *i.e.*, with the manner and degree of evidence required at the successive stages of the litigation." *See Lujan*, 504 U.S. at 561. At the pleading stage, "general factual allegations of injury resulting from the defendant's conduct may suffice." *Id.* In response to a summary judgment motion, however, the plaintiff can no longer rest on such mere allegations, but must set forth by "affidavit or other evidence 'specific facts'", which for purposes of the summary judgment motion will be taken to be true.[5] *Id.* (citing Fed. R. Civ. P. 56(e)).

[5] PMRS attached to its supplemental letter brief an affidavit of Edwin R. Thompson, PMRS's President, purporting to provide evidence that PMRS suffered an injury in fact. *See* (PMRS Letter, ECF No. 65-1). The affidavit provides no evidence to sustain such a showing. In any event, the Court's decision does not turn on any affidavits or lack thereof.

III

To show that the FDA's denial of its PSA constituted an injury in fact, PMRS must show that it suffered "an invasion of a legally protected interest" that is (a) concrete and particularized and (b) actual or imminent, not conjectural or hypothetical. *Lujan,* 504 U.S. at 560. For an injury to be "particularized," it "must affect the plaintiff in a personal and individual way." *Spokeo, Inc. v. Robins*, 136 S. Ct. 1540, 1548 (2016). Particularization is necessary to establish injury in fact, but it is not sufficient. An injury in fact must also be "concrete" and "*de facto*"; that is, it must actually exist. *Id.*

Allegations of possible future injury do not satisfy the requirements of Article III. "A threatened injury must be certainly impending to constitute injury in fact." *Whitmore v. Arkansas*, 495 U.S. 149, 158 (1990) (citations omitted). "[S]ome day intentions—without any description of concrete plans, or indeed even any specification of when the some day will be—do not support a finding of the 'actual or imminent' injury that our cases require." *Lujan*, 504 U.S. at 564.

Between its briefing and presentation at oral argument, PMRS put forth a number of arguments which can be distilled into four main points as to why the FDA's denial of PMRS's Petition for Stay constituted an injury in fact. PMRS's arguments are grounded not just in its disagreement with the FDA's approval of RoxyBond, but in PMRS's disappointment with FDA's denial of PMRS's own NDA.[6] That denial, however, is primarily why PMRS cannot show injury in fact.

[6] PMRS filed a separate lawsuit over the denial of its NDA. That litigation is before the United States Court of Appeals for the District of Columbia Circuit. *See* (Petition for Review Ex. A, ECF No. 70).

A

PMRS first contends that the FDA's action, in and of itself, satisfies the injury in fact requirement. PMRS claims that "[p]oint blank, PMRS suffers from a particularized and imminent injury due to FDA's denial of its PSA." (Pl. Resp. Opp'n Mot. Summ. J. at 4, ECF No. 40.) At first blush, FDA regulations could seemingly support this argument. Under 21 C.F.R. § 10.45(d)(1), "[i]t is the position of FDA . . . [that] an interested person is affected by, and thus has standing to obtain judicial review of final agency action[.]" Petitions for stay of action under 21 C.F.R. § 10.35 fall within the regulation. *See* 21 C.F.R. § 10.45.

Unfortunately for PMRS, it is not that easy; the mere denial of a petition for stay cannot confer standing on PMRS. Unlike an agency, "[a federal court's] authority to hear a case is limited by the standing requirements of the United States Constitution." *Competitive Enter. Inst. v. U.S. Dep't of Transp.*, 856 F.2d 1563, 1565 (D.C. Cir. 1988). "If the petitioner has no Article III concrete interest in receiving the relief requested before the agency," Congress has no power to "grant a petitioner a right to seek judicial review of an agency's decision to deny him relief." *Hydro Investors Inc.*, 351 F.3d 1192, 1197 (D.C. Cir. 2003) (citing *Gettman v. DEA*, 290 F.3d 430, 433 (D.C. Cir. 2002)). Because Congress cannot abrogate the requirements of Article III, this principle applies even if Congress gave the plaintiff a right to seek judicial review. *Id.* "Any other rule would allow Congress to create federal jurisdiction by the simple expedient of granting any party—no matter how far removed from the true controversy—a right to petition the agency, and then a right to seek judicial review if the agency denied the request." *Id.*

While the Court is unaware of any judicial decisions as to whether a denial of a petition for stay is enough to show injury in fact for purposes of Article III standing, courts have, in other contexts, found that an agency's mere denial of a petition is insufficient. *See Am. Sports Council v. U.S. Dep't of Educ.*, 850 F. Supp. 2d 288, 294 (D.D.C. 2012) (finding that a plaintiff does not have standing to sue based solely on the Department of Education's denial of a petition to repeal, amend and clarify rules); *Hydro*, 351 F.3d at 1194 (holding that Federal Energy Regulatory Commission's denial of a petition for review was not sufficient grounds to demonstrate Article III standing); *Wilcox Elec., Inc. v. FAA*, 119 F.3d 724, 728 (8th Cir. 1997) (reasoning that if the court deemed a party's loss of an agency proceeding sufficient for Article III injury in fact, "[the court] would enable plaintiffs lacking Article III standing at the outset of their protests to bootstrap their way into a federal court"). Similarly here, PMRS does not have standing based solely on the FDA's denial of its Petition.

B

PMRS next argues that the FDA's denial of its PSA constitutes an injury in fact because RoxyBond's approval will negatively impact PMRS's research and development. Specifically, PMRS claims harm because the FDA "could require" PMRS in the future to compare its own abuse-deterrent products to RoxyBond as part of the approval process. (Pl. Resp. Opp'n Mot. Summ. J. at 4, ECF No. 40.) Because of this possibility, PMRS contends that it suffered an "immediate harm [ ] as a developer, even without a drug on the market" because the "approval process is different, [and] irrevocably changed" as a result of RoxyBond's approval. (Hr'g Tr. 129:8–11, Nov. 28, 2018.)

FDA Guidance for evaluating abuse-deterrent opioid products provides that the FDA may require drug sponsors to "compare their formulations against approved abuse-deterrent versions of the same opioid." (FDA Guidance on Abuse-Deterrent Opioids, AR at FDA00756.) The Guidance also states that "[t]he standard against which each product's abuse-deterrent properties are evaluated will depend on the range of abuse-deterrent and non-abuse-deterrent products on the market at the time of that application." (*Id.* at FDA00736.)

That the FDA *could*, someday, compare one of PMRS's drugs to RoxyBond as part of the approval process is too speculative to constitute a concrete and imminent injury for the purposes of Article III standing. While a plaintiff need not "await the consummation of threatened injury to obtain preventive relief," they must "demonstrate a realistic danger of sustaining a direct injury as a result of" the challenged conduct or that the injury is "certainly impending." *Babbitt v. United Farm Workers Nat'l Union*, 442 U.S. 289, 298 (1979). Allegations of "possible future injury" are not sufficient. *Reilly v. Ceridian Corp.*, 664 F.3d 38, 42 (3d Cir. 2011) (citing *Whitmore*, 495 U.S. at 158). PMRS's concern that the FDA, at some undefined future time, could possibly deny a future drug application because it compares unfavorably to RoxyBond is the furthest thing from a "certainly impending" injury.[7]

[7] To the extent PMRS argues it was injured because the FDA compared PMRS's rejected NDA to RoxyBond, such an argument lacks any basis. There is no evidence that the FDA compared PMRS's proposed drug to RoxyBond when it denied PMRS's NDA. *See* (FDA Denial of PMRS's New Drug App., ECF No. 58-2). To the contrary, the application was denied for reasons separate and distinct from RoxyBond. *See supra* note 3.

C

PMRS also claims that RoxyBond's approval caused PMRS to sustain "competitive injuries". *See* (Pl. Resp. Opp'n Mot. Summ. J. at 2, ECF No. 40). PMRS alleges that RoxyBond unfairly benefited from the "first-mover advantage" because RoxyBond is the first opioid of its kind to reach the market. (Pl. Resp. Opp'n Mot. at 2, ECF No. 60.) Prior to RoxyBond's approval, there were no approved immediate release opioids with abuse-deterrent labeling. PMRS sought FDA approval for an immediate release, abuse-deterrent opioid with labeling for acute use. PMRS believes that the FDA unfairly "vault[ed]" RoxyBond over its proposed drug, *see* (Hr'g Tr. 20:2, 31:15, 35:2, 131:4) by "misapplying the FD&C Act, causing disparate results in how the products of developers are evaluated by FDA." (Pl. Resp. Opp'n Br. Sup. Summ. J. at 2, ECF No. 65.) RoxyBond's approval, PMRS contends, has decimated PMRS's potential "market share," "market position and/or market opportunities." *See* (Pl. Resp. Opp'n Mot. Summ. J. at 9, ECF No. 40). PMRS alleges that "once [RoxyBond] goes to market with labeling for chronic use, coupled with abuse deterrence, that's going to make it impossible for [PMRS], who has [an] acute use drug[,] to have any share of the market." (Hr'g Tr. 123:3–8.)

The competitor standing doctrine recognizes that "parties suffer constitutional injury in fact when agencies lift regulatory restrictions on their competitors or otherwise allow increased competition." *La. Energy and Power Auth. v. FERC*, 141 F.3d 364, 367 (D.C. Cir. 1998). A party seeking to establish standing on this basis "must demonstrate that it is a direct and current competitor whose bottom line may be adversely affected by the challenged government action." *KERM, Inc. v. FCC*, 353 F.3d

57, 60 (D.C. Cir. 2004). In the drug context, whether a company's drug has received at least tentative approval by the FDA is a "key factor in standing analysis." *Mylan Pharm. Inc. v. U.S. Food & Drug Admin.*, 789 F. Supp. 2d 1, 7 (D.D.C. 2011).

PMRS is not a "current" competitor with RoxyBond in the immediate release, abuse-deterrent opioid market for the basic reason that PMRS does not even have an approved drug in that market, something PMRS acknowledged at oral argument. *See* (Hr'g Tr. 19:18–20). PMRS's proposed drug was rejected by the FDA. (FDA Denial of PMRS's New Drug Application at 6, ECF No. 58-2.) In fact, the FDA found that PMRS failed to articulate sufficient grounds to even justify a hearing. (*Id.*) PMRS is merely a company that hopes to someday have a product to sell in this market. The first-mover advantage may well be valuable to a drug developer, *see Teva Pharm. USA, Inc. v. Sebelius*, 595 F.3d 1303, 1311 (D.C. Cir. 2010), but absent even a tentatively approved drug in the market, PMRS has not been injured because the FDA allowed a different drug to be the first to market.[8]

D

PMRS's final argument is that "[i]f PMRS's drug application is approved by the FDA in the short run, it will directly suffer from RoxyBond's improper labeling." (Pl. Resp. Opp'n Mot. Summ. J. at 7.) More specifically, as a result of the abuse-deterrent, chronic use labeling, PMRS claims that "[p]atients will be hesitant to be dispensed

[8] PMRS is seemingly frustrated that the FDA approved RoxyBond for chronic use, which PMRS contends lacks sufficient evidence and is therefore contrary to the Food, Drug & Cosmetic Act. PMRS asserts that "FDA's misapplication of the FD&C's 'substantial evidence' requirement resulted in a denial of one developer's application over another's to the detriment of the public." (Pl. Resp. Opp'n Br. Sup. Summ. J. at 3, ECF No. 65.) Even assuming, *arguendo*, that the FDA misapplied the statute to RoxyBond's application and that the FDA lacked sufficient evidence to approve RoxyBond's chronic use labeling, that would not constitute an injury in fact to PMRS, again because PMRS does not have a tentatively approved product in the market. *See Mylan*, 789 F. Supp. 2d at 7.

other IR opioids with dissimilar labeling to ROXYBOND because of the harm caused by that drug." *Id.* PMRS also claims that "patients are going to think that that drug is safer than the other immediate release drugs with labelling for chronic use on the market." (Hr'g Tr. 38:22–24.) Again, this argument for injury hinges on PMRS having an approved immediate release opioid. Since it doesn't, PMRS falls back on mere speculation over attenuated, hypothetical future contingencies.

IV

Because PMRS fails to demonstrate injury in fact, the Court need not explore whether PMRS has shown causation or redressability for Article III standing. Nor need the Court address the question of whether PMRS has met the prudential standing requirements.

An appropriate order follows.

BY THE COURT:

/s/ Gerald J. Pappert
GERALD J. PAPPERT, J.